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Insights of a Challenging Case: Lymphangioleiomyomatosis

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is progressive cystic lung disease that affects premenopausal women with the involvement of many organs of the body including the lungs. It commonly presents with dyspnea and cough, but its clinical course may be complicated by pleural effusions and recurrent pneumothorax. LAM is strongly associated with tuberous sclerosis complex (TSC) and may yield other clinically significant findings such as renal angiomyolipomas (AMLs) and lymphadenopathy. Investigations including radiological imaging, serum testing, and biopsies should be carefully considered when making a diagnosis as symptoms can be mistaken for other lung pathologies. The current mainstay of treatment is immunosuppressants and supportive therapy with bronchodilators and oxygen, while lung transplant is performed for end-stage disease.

This case report details an unusual presentation of a 20-year-old female diagnosed with sporadic LAM following a previous pulmonary tuberculosis infection. She had a history of recurrent bilateral pneumothorax following initiation of antitubercular treatment (ATT). Diagnosis was made on the basis of clinical presentation and computed tomography (CT) scans; in addition, histopathological examination of the cervical lymph nodes revealed coexisting extrapulmonary tuberculosis. A brief literature review of the relevant topics is also discussed in this report.

Keywords: Lymphangioleiomyomatosis; pneumothorax; angiomyolipomas; antitubercular treatment; immunosuppressants; histopathological

Introduction

Lymphangioleiomyomatosis (LAM) is a rare lung disease characterized by the proliferation of smooth muscle cells which can affect organs such as kidneys and lymphatics; however, it mainly results in cystic lung disease.[1] Typically, LAM affects women of reproductive age between the 4th and 5th decades of life and presents as unexplained dyspnea.[2] However, a third of patients also have concurrent spontaneous pneumothorax and 10-30% of patients may develop pleural effusion in the course of their disease.[3,4] Initial analysis of chest radiograph is usually inconclusive, and physical examination may reveal no abnormalities or less commonly, wheezing and/or crackles; this may result in a misdiagnosis of asthma of obstructive pulmonary disease and evade further clinical exploration.[5] High resolution computed tomography (HRCT) has higher sensitivity and specificity and is used as the standard imaging modality for LAM; CT abdomen and pelvis should also be considered to rule out the presence of renal angiomyolipomas (AMLs), a frequently associated finding.[6]

LAM can be grouped into a class of lung diseases called Diffuse Cystic Lung Disease (DCLD) that are characterized by diffuse spherical or irregularly shaped air spaces in the lungs bordered by thin walls. These have been divided based on CT findings and underlying etiologies; major criteria for division are grades of metastasis, lymphoproliferative nature, association with smoking, infections, and congenital defects.[7] It is further categorized based on mutations in tuberous sclerosis complex (TSC1 and TSC2), while sporadic LAM occurs when the mutation is only seen in the affected cells.[2] LAM can be mistaken as other DCLDs but is differentiated by multiple characteristic cysts on lung HRCT along with kidney AML, chylothorax or chylous effusion in abdomen, TSC mutation, lymph node involvement, and/or elevated vascular endothelial growth factor-D (VEGF-D).[8] An estimated 3 to 8 million women currently suffer from the disease.[9]

Case History

A 20-year-old unmarried female, non-smoker presented with a 10-month history of fever, shortness of breath, and weight loss. The fever was low grade in nature and the shortness of breath was gradual in onset; based on the Modified Medical Research Council (mMRC) dyspnea scale, it was progressive and increased from grade 2 to grade 3. She had no other complaints at the time of admission. The patient had a history of previous pulmonary tuberculosis 9 months back for which she took antitubercular treatment (ATT) for 6 months (2 months 4FDC + 4 months 2FDC) based on sputum grounds. In addition, she described visiting the emergency department in the past due to sudden onset of right sided chest pain and shortness of breath for 6 months. According to

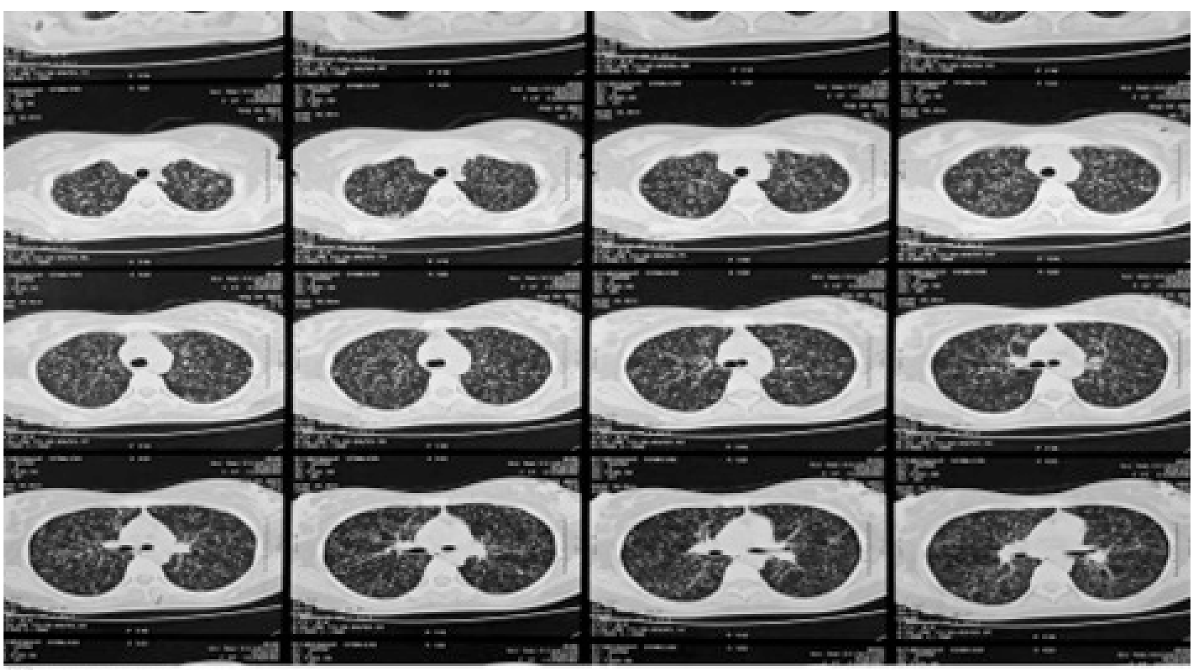

Figure 1A. HRCT

the chest radiograph, it showed right sided pneumothorax so tube thoracostomy was done. Following the procedure, pneumothorax was resolved, chest tube was extubated, and she was discharged.

After 2 weeks of discharge from the hospital, she developed recurrent ipsilateral pneumothorax, which was treated with right sided tube thoracostomy followed by pleurodesis. 3 months after this procedure, she developed left sided pneumothorax which was handled identically. At the time, HRCT showed numerous nodular, linear, and bilateral infiltrates that were identified diffusely across all lobes (Figure 1A & B). A few cystic cavities were seen in the apical posterior segment of the left upper lobe laterally, but airways were still patent with no effusions or pneumothorax. A few enlarged mediastinal lymph nodes and multiple prominent maxillary lymph nodes were seen. In addition, liver fatty infiltration and calculi were observed in both kidneys.

On examination, the patient was tachypneic, tachycardiac, and oxygen saturation at room air was found to be 85%; in addition, she displayed pallor and a right lower anterior cervical lymph node, roughly 2 cm in diameter, was palpable. Chest auscultation revealed bilateral fine crackles over multiple lung fields and the initial chest radiograph displayed bilateral interstitial nodular opacities (Figure 2). Baseline investigations were conducted afterward; complete blood count (CBC) showed leukocytosis, neutrophilia and lymphopenia while liver function tests (LFTs) exhibited raised alkaline phosphatase and total proteins.

HRCT was conducted again, which exhibited mild left sided pneumothorax as well as a loculated hypodense area with surrounding hyperdensity seen along the right hemothorax representative of calcified prior empyema or pleural thickening. There were multiple small pulmonary cysts of varying sizes throughout the lungs and multiple tiny discrete pulmonary nodules scattered in both lungs. In addition, there were fibrocalcific changes in the bilateral upper lobe and calcified mediastinal lymph nodes which were likely due to prior infection and less likely an atypical manifestation of cystic lung disease. These findings were highly suggestive of lymphangioleiomyomatosis (Figure 3A-D).

Following this procedure, CT abdomen and pelvis were

Figure 1B. HRCT: CT scan shows that there are numerous nodular and linear branching infiltrates giving tree in bud appearance.

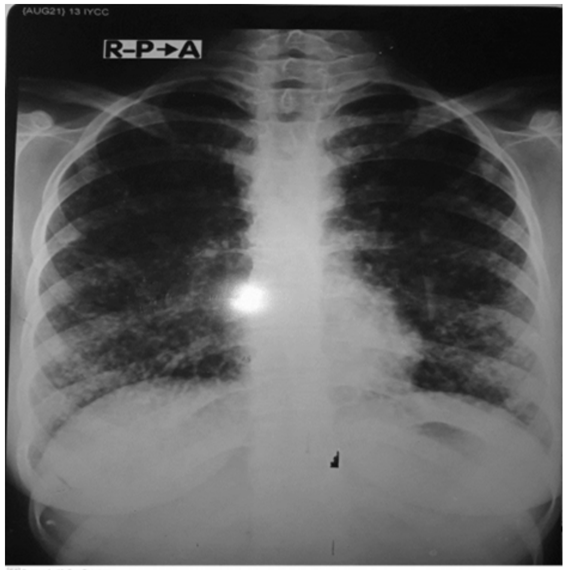

Figure 2. Chest X-Ray (PA) displaying bilateral interstitial nodular opacities

also ordered, showing multiple necrotic matted enlarged lymph nodes at the porta hepatis, celiac axis, precaval region, inter aortocaval region, the largest being 1.5 cm in diameter. The spleen appeared bulky and showed multiple peripherally enhancing cystic lesions, but liver and pancreas were normal. Both kidneys and adrenal glands appeared normal with no evidence of mass, calculus, or hydronephrosis observed. Finally, the sigmoid colon showed submucosal edema with luminal narrowing. Notably, typical associated findings of TSC-LAM such as renal AMLs and chylous effusions were not found.

Further investigation and management included a cervical node fine needle aspiration cytology (FNAC) conducted on clinical suspicion which showed multiple foci of tan-white tissue grossly. Microscopically, fibrocollagenous changes, lymphoid tissue focal hemorrhage, and epithelioid granulomata with caseous necrosis and giant cells were seen. Neutrophils, lymphocytes, histiocytes, and red blood cells were

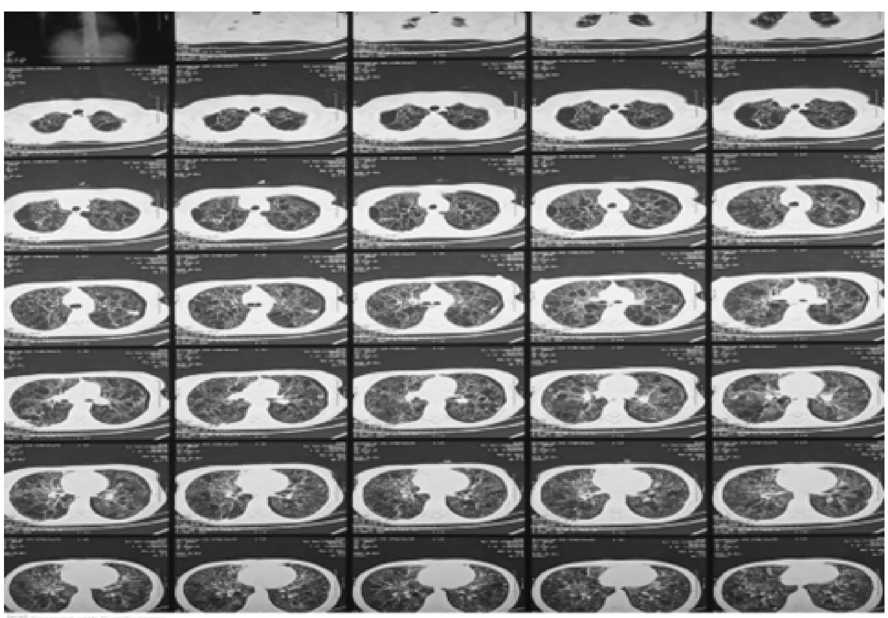

Figure 3A. HRCT showing diffuse pulmonary cysts and nodules of varying sizes scattered in both lungs, as well as left-sided pneumothorax

Figure 3B. HRCT

examined against a necrotic background and immunohistochemical stains CD3, CD20, and ki67 in this tissue showed a reactive pattern. These findings of necrotic chronic granulomatous inflammation led to suspicion of an infective etiology such as tuberculosis upon which acid fast-bacillus (AFB) and GeneXpert tissue biopsy was performed. The test was positive, confirming an additional diagnosis of extrapulmonary tuberculosis and resulting in the patient undergoing a new course of ATT.

Serum VEGF-D testing is not available in Pakistan and the patient was recommended a transbronchial lung biopsy for definitive confirmation of LAM, which she refused. Thus, the patient was advised to continue ATT and she was discharged after home oxygen therapy was arranged. Since her discharge, she has not reappeared for a follow-up visit.

Discussion

Our patient is a classic presentation of LAM in a woman of childbearing age. Previously, LAM was classified as an interstitial lung disease, but further studies into the genetics of the illness have led it to be classified as a low grade metastatic, destructive cancer by the World Health Organization (WHO). Neoplastic cells found in LAM were identified as originating from perivascular epithelial cells (PEC), leading to its classification as a PEComa or PEC tumor, which belongs to a family of mesenchymal tumors that also includes AMLs.[10] LAM results from proliferation of smooth muscle-like cells with inactivating mutations such as TSC1 and TSC2 which code for hamartin and tuberin, respectively.[11] These proteins play a role in suppressing abnormal growth and division and their underproduction results in the formation of benign tumors in multiple locations in the body, including AMLs in kidneys that are important for the diagnosis for LAM.[11]

As a result of these mutations, there is continuous activation of the mechanistic target of rapamycin (mTOR) signaling pathway, which leads to increased protein production and reduced autophagy.[12] Thus, multiplication of smooth muscle cells in bronchial walls and lymphatic vessels of the lungs leads to destruction of lung parenchyma and cyst formation.[13] The debate regarding the true origin of these cells is ongoing with two theories: the first proposing an airway or vascular origin, or from AML in the kidney which was transported via neoplastic dissemination.[10] The two main forms of LAM have been identified based on hereditary or sporadic TSC mutation, the latter being present in this case and in 80% of LAM patients.[5] Several studies report that TSC-LAM (mainly

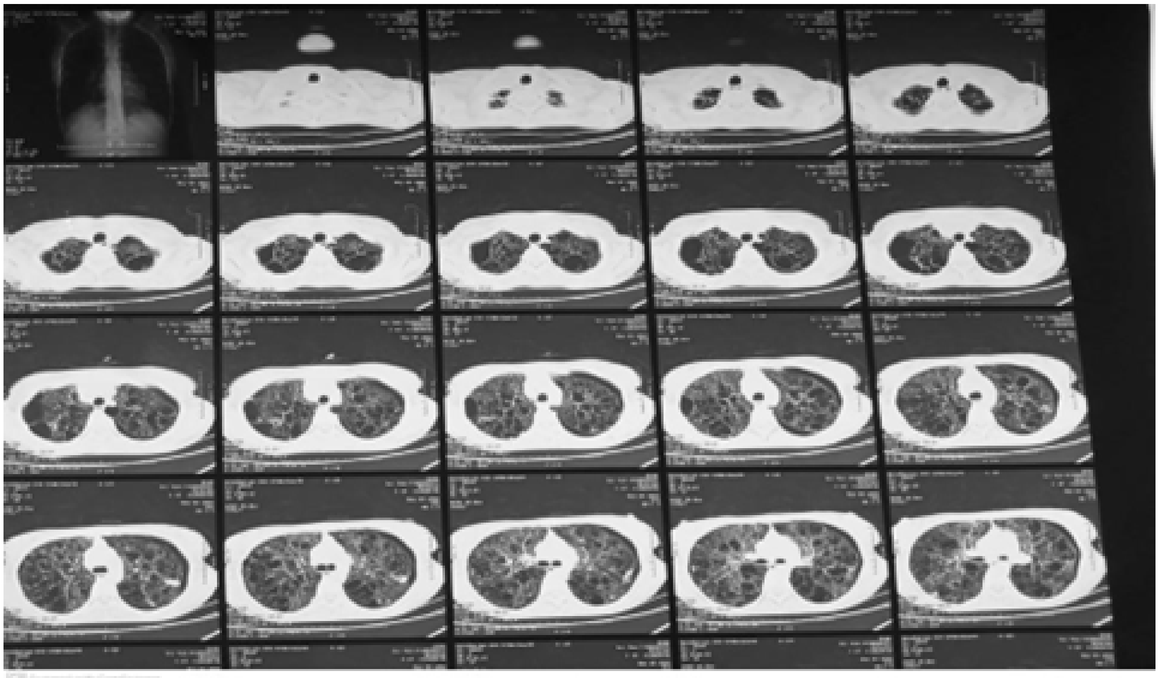

Fig 3C. HRCT

TSC2 mutation) is found among 26-50% women [14-17] and 10-38% of males with LAM.[18,19] However, almost all cases of sporadic LAM are in women, with the occurrence being 1 in 400,000 adult females.[9,20]

Diagnosis of LAM is based upon specific histological findings made with thoracoscopic biopsy or HRCT of thorax along with characteristic history and clinical symptoms.[3] In most cases, tissue biopsy is not required for definitive diagnosis of LAM because this condition has a distinctive CT appearance. HRCT findings show multiple (>10) diffuse thin-walled air-filled cysts of varying size scattered throughout lung parenchyma.[21] Other complications include chylous effusion, pneumothorax, lymphadenopathy, and renal AML.[22] In addition to this, immunohistochemical staining on a transbronchial lung biopsy specimen is done for alpha actin, desmin, estrogen, progesterone, and HMB-45 which will further confirm the diagnosis.[6] The normal smooth muscle in the lung is unreactive with HMB-45 which makes it a sensitive marker for LAM whereas the presence of actin, desmin, and vimentin is expressed both in LAM and normal smooth muscle cells.[23] Serum levels of VEGF-D, equal to or greater than 800 pg/mL have become accepted due to their extremely rare occurrence in other cystic diseases.[7,22] Effective treatment and management should be offered after the diagnosis of LAM.

The most effective drug in the treatment of LAM is the immunosuppressant sirolimus, an mTOR inhibitor, which directly inhibits T-cell proliferation and abnormal growth of smooth muscle cells in lung parenchyma, thus slowing progression of the disease and minimizing complications.[6,13] The U.S. Food and Drug administration (FDA) approved RAPAMUNE (sirolimus) as the first treatment for LAM in 2015 after conducting the Multicenter International LAM Efficacy of Sirolimus (MILES) trial in which patients were treated with either sirolimus or placebo for 1 year; results showed that those treated with sirolimus had stabilized lung function and reduced levels of serum VEGF-D.[24,25] However, this medication has several adverse side effects such as nausea, mouth ulcers, diarrhea, swelling of hands or feet, high cholesterol, and dizziness;[25] in addition, this drug is of limited availability in Pakistan and is not affordable for all patients. Instead, supportive treatment can be provided in this case with bronchodilators and oxygen therapy to assist in respiration.[2] Currently, the only definitive treatment for progressive LAM with worsening symptoms and deteriorating lung function is lung transplant.[2,6] Generally, patients undergo pleurodesis to prevent chances of recurrent pneumothorax; however, with prior pleurodesis there is an increased risk of bleeding and prolonged operating time, but this does not necessarily contraindicate lung transplant.[26]

Tuberculosis (TB), on the other hand, remains a worldwide emergency with an estimated 25% of the global population being currently infected and 10 million new infections diagnosed each year [27]. Pakistan ranks fifth in the global TB burden, with 339,256 new and relapsed cases being reported and bringing the country's total TB incidence to 611,000 in 2021.[28] It has two main clinical

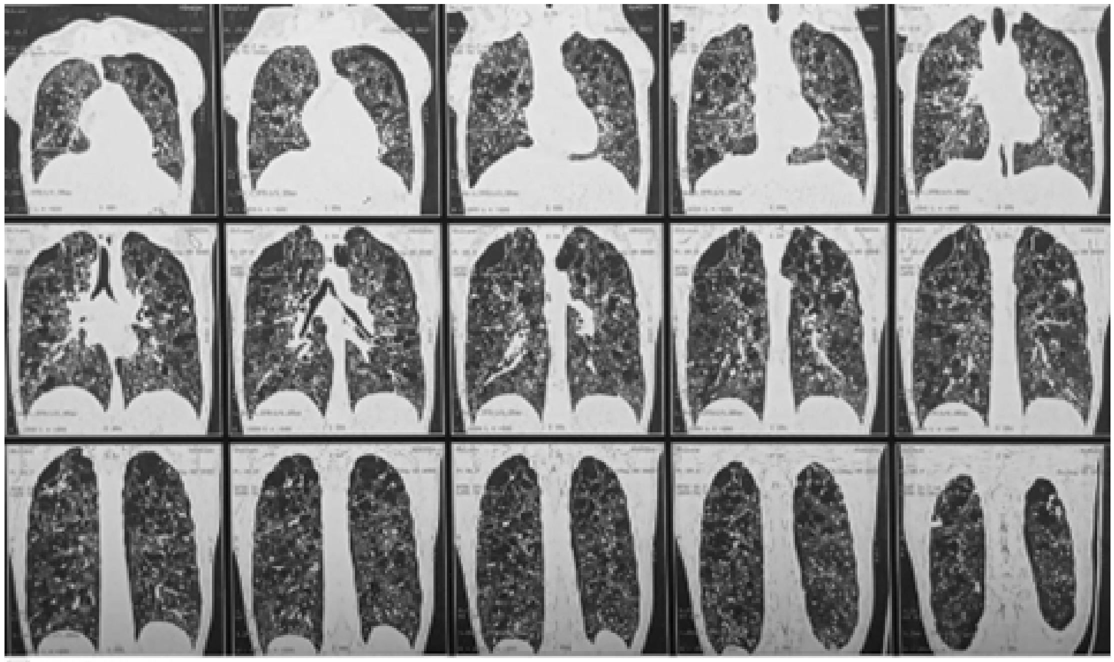

Fig 3D. HRCT

presentations: pulmonary tuberculosis with symptoms of cough, fever, night sweats, fatigue, and hemoptysis or extrapulmonary and disseminated tuberculosis, which are of many varieties with symptoms unique to the organ(s) or organ system(s) involved.[27] A 2016 retrospective study conducted in Pakistan reported that the most common manifestations of extrapulmonary tuberculosis included pleural, lymphatic, abdominal, osteoarticular, and central nervous system (CNS) involvement;[29] our patient had predominantly lymphatic and abdominal findings on radiological and microscopic investigation. In addition, latent infection may undergo reactivation in response to immune suppression, aging, or the presence of an intercurrent disease. Reports suggest that the presence of longstanding illness caused by Mycobacte-rium tuberculosis is associated with multiple human diseases such as other pulmonary pathology (pneum-onia, chronic obstructive pulmonary disease [COPD], lung cancer), autoimmune disease (sarcoidosis and syst-emic lupus erythematosus [SLE]), and metabolic syndro-mes including diabetes, obesity, and atherosclerosis.[30]

However, there is currently little data to prove any correlation between cystic lung disease and pulmonary tuberculosis; in fact, there is only one published case of new infection in a patient with previously diagnosed TSC-LA.[11] To the best of our knowledge, this is a unique presentation and the first case with an overlap of tuberculosis and LAM following the pulmonary infection earlier in life; as such, there is no known literature that suggests that the pathogen may be a risk factor for the development of DCLD or that it has a role in inciting the underlying pathology. We intend this case to provide insight into or increase clinicians' understanding of both diseases and provide a basis for further research and investigation of unusual pulmonary pathology.

Conclusion

Lymphangioleiomyomatosis is a cystic lung disease occurring in women of childbearing age which can affect multiple organs in the body. It is sporadic in nature or associated with tuberous sclerosis complex, while an infection with Mycobacterium tuberculosis can lead to comorbidity with a plethora of illnesses in the long term. A rare presentation with both diseases occurring in proximity to each other should warrant extensive investigation to secure a diagnosis and begin adequate treatment. This includes conducting routine imaging studies that show a distinctive cystic pattern, immunohistochemical staining, measuring specific serum protein levels such as VEGF-D, and microscopic examination of biopsy specimens. Though advances are ongoing, oxygen therapy and immunomodulators are the current mainstay of treatment for LAM.

References

1. Rhee JA, Adial A, Gumpeni R, Iftikhar A, Rhee JA. Lymphangioleiomyomatosis: a case report and review of literature. Cureus. 2019;11(1).

2. O'Mahony AM, Lynn E, Murphy DJ, Fabre A, McCarthy C. Lymphangioleiomyomatosis: a clinical review. Breathe (Sheff). 2020;16(2):200007.
3. Ryu JH, Moss J, Beck GJ, Lee JC, Brown KK, Chapman JT, Finlay GA, et al. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. Am J Res Crit Care Med. 2006;173(1):105-11.
4. Johnson SR. Lymphangioleiomyomatosis. Eur Respir J. 2006;27.
5. McCarthy C, Gupta N, Johnson SR, Yu JJ, McCormack FX. Lymphangioleiomyomatosis: pathogenesis, clinical features, diagnosis, and management. Lancet Respir Med. 2021.
6. Johnson SR. Lymphangioleiomyomatosis. Eur Respir J. 2006;27(5):1056-65.
7. Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. Diffuse Cystic Lung Disease. Part I. Am J Respir Crit Care Med. 2015;191(12):1354-66.
8. Taylor JR, Ryu J, Colby TV, Raffin TA: Lymphangioleiomyomatosis. N Engl J Med. 1990, 323:1254-60.
9. Harknett EC, Chang WY, Byrnes S, Johnson J, Lazor R, Cohen MM, et al. Use of variability in national and regional data to estimate the prevalence of lymphangioleiomyomatosis. QJM: An Int J Med. 2011;104 (11):971-9.
10. Sathirareuangchai S, Shimizu D, Vierkoetter KR. Pulmonary lymphangioleiomyomatosis: a case report and literature review. Hawaii J Health Soc Welf. 2020;79(7):224.
11. Lewandowska K, Oniszh K, Kope EA, Röhrenschef1 PR, Ku J. Bacteriologically confirmed pulmonary tuberculosis in a patient with lymphangioleiomyomatosis accompanying tuberous sclerosis syndrome. Via Medica. 2011; 309-314.
12. Steagall WK, Pacheco-Rodriguez G, Darling TN, Torre O, Harari S, Moss J. The lymphangioleiomyomatosis lung cell and its human cell models. Am J Respir Cell Mol Biol. 2018;58(6):678–83.
13. Cong CV, Anh TT, Ly TT, Duc NM. Pulmonary lymphangioleiomyomatosis (LAM): A literature overview and case report. Radiol Case Rep. 2022;17(5).
14. Henske EP, McCormack FX. Lymphangioleiomyomatosis – a wolf in sheep's clothing. J Clin Invest. 2012; 122: 3807–3816.
15. Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. Mayo Clin Proc. 2000;75((6)):591–594.
16. Franz DN, Brody A, Meyer C, Leonard J, Chuck G, Dabora S, et al. Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med. 2001;164(4):661-8.
17. Cudzilo CJ, Szczesniak RD, Brody AS, Rattan MS, Krueger DA, Bissler JJ, et al. Lymphangioleiomyomatosis screening in women with tuberous sclerosis. Chest. 2013;144:578–585.
18. Muzykewicz DA, Sharma A, Muse V, Numis AL, Rajagopal J, Thiele EA. TSC1 and TSC2 mutations in patients with lymphangioleiomyomatosis and tuberous sclerosis complex. J Med Genet. 2009;46((7):465–468.
19. Ryu JH, Sykes AM, Lee AS, Burger CD. Cystic lung disease is not uncommon in men with tuberous sclerosis complex. Respir Med. 2012;106(11):1586-90.
20. Urban T, Lazor R, Lacronique J, Murris M, Labrune S, Valeyre D, et al. Pulmonary lymphangioleiomyomatosis A study of 69 patients Groupe d'Etudes et de Recherche sur les Maladies “Orphelines” Pulmonaires (GERM“O“P) Medicine (Baltimore) 1999;78:321–37.
21. Johnson SR, Cordier JF, Lazor R, Cottin V, Costabel U, Harari S, et al. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J. 2010;35 (1):14-26.
22. Bearz A, Rupolo M, Canzonieri V, Balestreri L, La Mura N, Berretta M, et al. Lymphangioleiomyomatosis: A case report and review of the literature. Tumori. 2004;90:528–531.
23. Bonetti F, Chiodera PL, Pea M, Martignoni G, Bosi F, Zamboni G, et al. Transbronchial biopsy in lymphangiomyomatosis of the lung. HMB45 for diagnosis. Am J Surg Pathol. 1993;17(11):1092-102.
24. McCormack FX, Inoue Y, Moss J, Singer LG, Strange C, Nakata K, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Eng J Med. 2011;364 (17):1595-606.
25. Pfizer's RAPAMUNE® (sirolimus) Becomes First FDA-Approved Treatment for Lymphangioleiomyomatosis (LAM), A Rare Progressive Lung Disease. 2015. Pfizer. Available from URL: https://www.pfizer.com/news/press-release/press-release-detail/pfizer_s_rapamune_sirolimus_becomes_first_fda_approved_treatment_for_lym phangioleiomyomatosis_lam_a_rare_progressive_lung_disease.
26. Kania BE, Jain S, West B, Courtney SW. Lymphangioleiomyomatosis: A Case Report and Review of Clinical Features and Management. Cureus. 2020;12

(6):e8386.

27. Suárez I, Fünger SM, Kröger S, Rademacher J, Fätkenheuer G, Rybniker J. The Diagnosis and Treatment of Tuberculosis. Dtsch Arztebl Int. 2019; 116(43):729-735.
28. World Health Organization. Global Tuberculosis Report. World Health Organization. 2022. Available from URL: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/globaltuberculosis-report-2022.
29. Tahseen S, Khanzada FM, Baloch AQ, Abbas Q, Bhutto MM, Alizai AW, et al. (2020) Extrapulmonary tuberculosis in Pakistan- A nationwide multicenter retrospective study. PLoS ONE.15(4): e0232134.
30. Chai Q, Zhang Y and Liu CH. Mycobacterium tuberculosis: An Adaptable Pathogen Associated with Multiple Human Diseases. Front Cell Infect. Microbiol. 2018;8:158.